Safety of steroids in severe community-acquired pneumonia

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In sCAP, corticosteroids likely increase the risk of hyperglycaemia. Their effects on other adverse events, including secondary infections and GI bleeding, require further study. In addition, there is limited information about long-term side-effects. https://bit.ly/3AvE8rM

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Abstract

The systemic use of corticosteroids for patients with severe community-acquired pneumonia (sCAP) remains controversial in clinical practice, particularly in terms of the safety profile of these drugs. This narrative review aims to analyse the available literature data concerning the safety of short-term steroid use in the treatment of sCAP, while also highlighting potential future research directions. Several trials and meta-analyses have evaluated corticosteroid therapy as an adjuvant treatment for sCAP, yielding heterogeneous results regarding its efficacy and safety. Despite the wide variability in results, it is generally accepted that steroids are not associated with a significant risk of healthcare-associated infections, gastrointestinal bleeding or acute kidney injury in patients with sCAP in the short term. Nevertheless, such drugs are linked to hyperglycaemia, necessitating regular monitoring and appropriate management. The influence of steroids on long-term outcomes and their potential risks in viral sCAP still needs to be investigated.

Introduction

Severe community-acquired pneumonia (sCAP) remains a significant global health challenge.

Despite advances in antimicrobial therapy and life-support measures, the prognosis for sCAP has persistently deteriorated in recent years, with a mortality rate ranging from 13 to 36% [1]. The risk is particularly elevated in patients presenting with shock, requiring invasive mechanical ventilation or experiencing a combination of both factors [2, 3].

Pneumonia may cause severe pulmonary and systemic inflammation, leading to compromised gas exchange, sepsis, organ failure and an increased risk of mortality. Glucocorticoids, also called steroids or corticosteroids, exhibit potent anti-inflammatory and immunomodulatory properties, potentially mitigating the impact of pneumonia. Several randomised controlled trials (RCTs) (table 1) [4–12] have investigated the role of adjunctive steroids in the treatment of sCAP and have demonstrated beneficial effects [4, 6, 8–11], such as reduced mortality. However, their overall effectiveness remained uncertain until the trial reported by Dequin *et al.* [4]. Indeed, the latest guidelines from the European Respiratory Society (ERS)/European Society of Intensive Care Medicine (ESICM)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Latin American Thoracic Association (ALAT) [13], published before the trial, recommend their use only in cases of sCAP associated with septic shock. Dequin *et al.* [4] demonstrated that intravenous hydrocortisone treatment in sCAP patients reduced 28-day mortality compared to placebo, suggesting that corticosteroid therapy should be considered in all sCAP cases, not just in those with septic shock. Following this favourable trial, hydrocortisone at a dosage of 200 mg every 24 h for 4–7 days has been deemed reasonable.

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TABLE 1 Characteristics of the most pertinent randomised controlled trials (RCTs) assessing corticosteroid treatment in patients with severe community-acquired pneumonia (sCAP)

Study	Year	Study site	Design	Patients	Regimen of corticosteroid	Number of patients		Primary outcome
						Intervention	Control	
Dequin *et al.* [4]	2023	31 centres in France	Double-blind RCT	Adult patients with sCAP[#] requiring ICU admission	Hydrocortisone, 200 mg *i.v.* for 4 days, then tapered in 4 or 10 days according to pre-specified plan based on patient's improvement	400	395	Reduction in 28-day mortality
Meduri *et al.* [5]	2022	42 centres in USA	Double-blind, randomised, placebo-controlled clinical trial	Adult patients with sCAP[#] requiring ICU admission	Methylprednisolone, 40 mg *i.v.* loading followed by 40 mg·day^{-1} through day 7 and progressive tapering for 20 days	297	287	No reduction in 60-day mortality
Heming *et al.* [6] **subgroup analysis of the APROCCHSS RCT** [7]	2018	34 centres in France	Double-blind, randomised, placebo-controlled clinical trial	Adult patients with CAP-related septic shock requiring ICU admission	Hydrocortisone, 50 mg *i.v.* every 6 h and fludrocortisone, 50 µg *p.o.* once daily for 7 days	283	279	Reduction in 90-day mortality
Torres *et al.* [8]	2015	Three centres in Spain	Double-blind, randomised, placebo-controlled clinical trial	Adult patients with sCAP[#]	Methylprednisolone 0.5 mg·kg^{-1} *i.v.* every 12 h for 5 days	61	59	Reduction in treatment failure rate[¶]
Sabry *et al.* [9]	2011	Two centres in Egypt	Double-blind, randomised, controlled trial	Adult patients with sCAP[#] requiring ICU admission	Hydrocortisone, loading dose of 200 mg *i.v.*, followed by 300 mg daily for 7 days	40	40	Improvement in P_{aO_2}:F_{IO_2} and SOFA score by day 8 and reduction in the development of delayed septic shock
El Ghamrawy *et al.* [10]	2006	One centre in Saudi Arabia	Double-blind, randomised, controlled trial	Adult patients with sCAP[#] requiring ICU admission	Hydrocortisone, 200 mg *i.v.* bolus, followed by 240 mg daily for 7 days	17	17	ND
Confalonieri *et al.* [11]	2005	Six centres in Italy	Double-blind, randomised, placebo-controlled clinical trial	Adult patients with sCAP[#] requiring ICU admission	Hydrocortisone, 200 mg *i.v.* bolus, followed by infusion at a rate of 10 mg·h^{-1} for 7 days	23	23	Improvement in P_{aO_2}:F_{IO_2} and mortality[+]
Marik *et al.* [12]	1993	One centre in USA	Double-blind, randomised, placebo-controlled clinical trial	Adult patients with sCAP[#] requiring ICU admission	Hydrocortisone, 10 mg·kg^{-1} *i.v.* once	14	16	No effect on the serum TNF-α levels

[#]: Patients with sCAP, intensive care unit (ICU)-admitted patients who required mechanical ventilation or haemodynamic support. [¶]: Composite outcome of early and late treatment failure, or both. Early failure defined as 1) development of shock, 2) need for invasive mechanical ventilation not present at baseline and 3) death within 72 h of treatment. Late failure defined as 1) radiographic progression, 2) persistence of severe respiratory failure, 3) development of shock, 4) new need for invasive mechanical ventilation and 5) death between 72 h and 120 h after treatment initiation. [+]: Mortality outcome definition: 28 days, in hospital, and 60-days all-cause mortality. CAP: community-acquired pneumonia; F_{IO_2}: inspiratory oxygen fraction; ND: not defined; P_{aO_2}: arterial oxygen tension; SOFA: Sepsis-related Organ Failure Assessment; TNF-α: tumour necrosis factor-α.

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While long-term corticosteroid use is associated with well-known side-effects, the potential complications of short-term corticosteroid use are not as well understood and there is generally insufficient evidence available to guide clinicians. As a consequence, some clinicians avoid prescribing corticosteroids during active infections due to the recognised immunosuppressive effects and concerns about potential complications.

The aim of this review is to analyse literature data concerning the safety of short-term steroid use in sCAP treatment (table 2), specifically focusing on identifying known short- and long-term adverse events and their incidence rates.

Search strategy

A total of 50 articles were identified through a PubMed search of English language abstracts and articles published between January 1990 and March 2024.

RCTs, observational studies, translational studies and systematic and narrative reviews were retrieved. The keywords included "corticosteroids", "severe community acquired pneumonia", "viral community acquired pneumonia", "safety" and "adverse effects". These keywords were used alone and in combinations. The reference lists of original articles, narrative reviews, clinical guidelines and previous systematic reviews and meta-analyses were searched for additional relevant materials. The citations from the articles identified in these searches were also reviewed and included, where appropriate.

Articles were selected based on their relevance to the topic of corticosteroid safety in sCAP. Specifically, we focused on studies that reported on adverse effects, such as healthcare-associated infections (HAIs), hyperglycaemia, gastrointestinal (GI) bleeding and acute kidney injury (AKI). Articles were chosen based on the quality of the study design (*e.g.*, RCTs and large observational studies were prioritised) and relevance to both short- and long-term safety outcomes.

The decision to include papers from 1990 onwards was made to ensure a comprehensive analysis of the literature, particularly given that earlier studies on corticosteroids in pneumonia laid the groundwork for understanding their safety profile. While clinical practice has evolved, earlier trials provided important insights into corticosteroid mechanisms and complications, which remain relevant to modern treatment protocols. Additionally, older studies often serve as a comparison point for more recent trials, allowing us to examine how clinical evidence and treatment strategies have progressed over time.

Safety of steroids in sCAP

Differentiating outcomes across clinical trials

The adjunctive use of corticosteroids is currently part of standard management in several conditions such as COPD, tuberculosis and septic shock. However, the role of corticosteroids in the management of sCAP remains controversial, despite continuous research. The question of whether corticosteroids reduce mortality and improve clinical outcomes in sCAP is crucial, as is determining which patients are most likely to benefit, in order to appropriately weigh the risks against the potential benefits.

Currently, there is no universally accepted definition of sCAP, although it generally refers to intensive care unit (ICU)-admitted patients who require mechanical ventilation or haemodynamic support. According to the most recent ERS guidelines [13], corticosteroids are recommended only for sCAP patients with septic shock, given the limited evidence for mortality reduction in the broader population. However, this focus on mortality may overlook other clinically significant outcomes.

Most RCTs on community-acquired pneumonia (CAP) focus on outcomes such as clinical cure or treatment failure rather than mortality. For example, in a cohort with sCAP and high inflammation (C-reactive protein (CRP)>150 mg·L^{-1}), Torres *et al*. [8] demonstrated that methylprednisolone reduced treatment failure from 31% to 13%, largely by reducing late-treatment failures (occurring between 72 and 120 h). Similarly, Blum *et al*. [17] found that corticosteroids accelerated clinical recovery. In contrast, Snijders *et al.* [18] did not observe a significant impact on clinical cure after 7 days, likely due to the inclusion of less severe CAP cases and lower steroid doses in their trial. Additionally, Snijders *et al.* [18] noted that corticosteroids increased the incidence of late-treatment failures in nonsevere CAP patients, highlighting potential risks in this subgroup.

Meijvis *et al.* [19] also demonstrated that corticosteroids (dexamethasone) marginally reduced hospital stay duration, but the only RCT showing a clear reduction in 28-day mortality was the CAPE COD trial conducted by Dequin *et al.* [4], using hydrocortisone in sCAP patients. Importantly, Meduri *et al.* [5], in

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TABLE 2 Summary of adverse events (AEs) reported in randomised controlled trials

AE	Study	Type of corticosteroid used	Definition used	Increased risk of AE (yes/no)	Results		
					Steroids	Placebo	p-value
Healthcare-acquired infections	Dequin *et al.* [4]	Hydrocortisone	Infections (ventilator-associated pneumonia and bloodstream infection) that patients develop after being admitted to the hospital, specifically within 28 days of admission	No	39/400 (10%)	44/395 (11%)	0.54
	Meduri *et al.* [5]	Methylprednisolone	Nosocomial infections as defined in the guidelines for evaluation of new fever in critically ill adult patients [14]#	No	73/297 (25%)	76/287 (26%)	0.60
	Heming *et al.* [6]	Hydrocortisone +fludrocortisone	⩾1 episode of superinfection by day 180; site of superinfection: lung, blood, catheter-related, urinary tract, other	No	88/319 (28%)	77/329 (23%)	0.22
	Torres *et al.* [8]	Methylprednisolone	Patients tested positive for a nosocomial infection of any source	No	1/61 (2%)	0/59 (0%)	>0.99
	El Ghamrawy *et al.* [10]	Hydrocortisone	ND	No	2/17 (12%)	1/17 (6%)	NC
	Confalonieri *et al.* [11]	Hydrocortisone	ND	No	0/23 (0%)	4/23 (18%)	0.11
Hyperglycaemia	Dequin *et al.* [4]	Hydrocortisone	Median daily dose of insulin by day 7 in patients receiving insulin therapy (IQR): UI·day^{-1}	Yes	35.5 (15–57.5)	20.5 (9.4–48.5)	<0.0001
	Meduri *et al.* [5]	Methylprednisolone	An increase in blood glucose levels requiring the initiation or intensification of insulin therapy	No	46/297 (15%)	33/287 (11%)	0.16
	Heming *et al.* [6]	Hydrocortisone +fludrocortisone	⩾1 episode of blood glucose levels ⩾150 mg·dL^{-1} by day 7	No	280/319 (88%)	272/329 (83%)	0.08
			Number of days with ⩾1 episode of blood glucose levels ⩾150 mg·dL^{-1} by day 7	Yes	4.1±2.5	3.2±2.5	<0.001
	Torres *et al.* [8]	Methylprednisolone	ND	No	11/61 (18%)	7/59 (12%)	0.34
	Nafae *et al.* [15]	Hydrocortisone	Uncontrolled diabetes mellitus (glucose >250 mg·dL^{-1})	No	19/60 (32%)	8/20 (40%)	>0.05
	Fernández-Serrano *et al.* [16]	Methylprednisolone	Hyperglycaemia requiring insulin for adequate diabetes control	No	1/23 (4%)	0/22 (0%)	NC
Gastrointestinal bleeding	Dequin *et al.* [4]	Hydrocortisone	ND	No	9/400 (2%)	13/395 (3%)	NC
	Meduri *et al.* [5]	Methylprednisolone	ND	No	9/297 (3%)	5/287 (2%)	0.31
	Heming *et al.* [6]	Hydrocortisone +fludrocortisone	Gastroduodenal bleeding not otherwise specified	No	25/319 (8%)	21/329 (6%)	0.47
	Torres *et al.* [8]	Methylprednisolone	ND	No	0/61 (0%)	1/59 (2%)	0.50
	Nafae *et al.* [15]	Hydrocortisone	ND	No	1/60 (1.6%)	1/20 (5%)	>0.05
	Fernández-Serrano *et al.* [16]	Methylprednisolone	ND	No	1/23 (4%)	0/22 (0%)	NC
	Sabry *et al.* [9]	Hydrocortisone	ND	No	2/40 (5%)	2/40 (5%)	NC
	El Ghamrawy *et al.* [10]	Hydrocortisone	ND	No	2/17 (12%)	1/17 (6%)	NC
	Confalonieri *et al.* [11]	Hydrocortisone	Upper gastrointestinal bleeding diagnosed based on clinical criteria	No	1/23 (4%)	1/23 (4%)	1.0

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TABLE 2 Continued

AE	Study	Type of corticosteroid used	Definition used	Increased risk of AE (yes/no)	Results		
					Steroids	Placebo	p-value
Acute kidney injury	Meduri *et al.* [5]	Methylprednisolone	Acute renal failure requiring dialysis	No	15/297 (5%)	13/287 (5%)	0.77
	Torres *et al.* [8]	Methylprednisolone	ND	No	8/61 (13%)	8/59 (14%)	0.85
	Sabry *et al.* [9]	Hydrocortisone	ND	No	0/40 (0%)	6/40 (15%)	NC
	Confalonieri *et al.* [11]	Hydrocortisone	Serum creatinine greater than 2 $mg \cdot dL^{-1}$	No	0/23 (0%)	3/23 (13%)	0.23
Hospital readmission rate	Meduri *et al.* [5]	Methylprednisolone	Any rehospitalisation within 12 months	No	135/253 (53%)	120/250 (48%)	1.0
Adverse cardiac events	Meduri *et al.* [5]	Methylprednisolone	New serious atrial or ventricular arrhythmia not otherwise specified	No	34/297 (12%)	21/287 (7%)	>0.05
	Confalonieri *et al.* [11]	Hydrocortisone	Arrhythmia not otherwise specified	No	1/23 (4%)	3/23 (13%)	0.61
	Sabry *et al.* [9]	Hydrocortisone	Arrhythmia not otherwise specified	No	0/40 (0%)	1/40 (4%)	NC
Neuropsychiatric complications	Meduri *et al.* [5]	Methylprednisolone	Acute psychosis (emotional lability, anxiety, agitation, auditory and visual hallucinations)	No	14/297 (5%)	14/287 (5%)	0.93
	Torres *et al.* [8]	Methylprednisolone	Delirium not otherwise specified	No	1/61 (2%)	0/59 (0%)	>0.99
Acute hepatic failure	Meduri *et al.* [5]	Methylprednisolone	Acute liver function test abnormalities	No	11/297 (4%)	6/287 (2%)	0.25
	Torres *et al.* [8]	Methylprednisolone	ND	No	1/61 (2%)	0/59 (0%)	>0.99
	Confalonieri *et al.* [11]	Hydrocortisone	ND	No	0/23 (0%)	1/23 (4%)	NC

[#]: According to these guidelines, nosocomial infections are 1) infections that develop after 48 h of hospital admission, distinguishing them from community-acquired infections, 2) often associated with factors such as the use of invasive devices (*e.g.* catheters and ventilators) and exposure to the hospital environment, and 3) include infections such as ventilator-associated pneumonia, bloodstream infections and urinary tract infections. IQR: interquartile range; NC: not calculated; ND: not defined.

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the largest RCT on corticosteroids in CAP to date (ESCAPe trial), found no significant reduction in 60-day mortality, underscoring the complexity of interpreting these findings.

Differences in the inclusion criteria and timing of corticosteroid administration may explain the divergent outcomes between the trials conducted by Meduri *et al.* [5] and Dequin *et al.* [4]. For instance, the CAPE COD trial [4] excluded patients with viral CAP, based on data suggesting that corticosteroids may worsen outcomes in influenza-related pneumonia. Moreover, the ESCAPe trial [5] allowed randomisation up to 72–96 h after hospital admission, while in the CAPE COD trial, hydrocortisone was administered within 24 h of meeting severity criteria. The timing of corticosteroid initiation may be crucial, as early intervention could capitalise on the anti-inflammatory effects of glucocorticoids.

Interestingly, secondary outcomes in the Meduri *et al.* [5] trial indicated that corticosteroid treatment was linked to faster vasopressor withdrawal, quicker improvement in gas exchange for mechanically ventilated patients and more rapid decreases in inflammatory cytokines and fever resolution.

An important challenge in reaching evidence-based conclusions from these trials remains in the diversity of study designs, particularly in the variability of patient populations and inclusion/exclusion criteria, as well as the differences in treatment durations, steroid dosages and types of corticosteroids used. This lack of uniformity makes it difficult to establish which treatment regimen is truly optimal and in which specific subpopulations it may be most effective. While more recent studies, such as the ESCAPe [5], CAPE COD [4] and Torres *et al.* [8] trials, have employed rigorous and standardised criteria to improve patient selection, with well-defined disease severity markers (*e.g.*, CRP levels) and scoring systems (*e.g.*, CURB-65 (confusion, blood urea nitrogen levels, respiratory rate, blood pressure and age) or arterial oxygen tension/inspiratory oxygen fraction ratios) and more controlled protocols for dosage and duration, earlier studies, including those by Confalonieri *et al.* [11] and Marik *et al.* [12], exhibited greater variability in patient selection and corticosteroid dosing.

In conclusion, corticosteroids may significantly reduce long-term mortality in sCAP and appear to improve short-term outcomes, particularly in patients with high inflammatory markers and when administered early. Thus, corticosteroid therapy should not be limited to patients with septic shock alone, but also offered to those presenting with elevated inflammation (*e.g.*, high CRP). However, these findings should not be extrapolated to nonsevere CAP, where the literature remains inconsistent and where corticosteroids may even increase the risk of treatment failure.

There is an increasing need to stratify patients into distinct phenotypes, aided by biomarkers, to better identify which subsets of sCAP patients are likely to benefit from corticosteroid therapy, balancing risks and benefits appropriately.

Short-term side-effects

Steroid-related HAIs: incidence and risk factors

Clinicians' hesitation regarding the administration of corticosteroids is primarily due to the potential risk of secondary infections. Despite the efficacy of corticosteroids in mitigating excessive inflammatory responses, their immunosuppressive effects raise concerns regarding their use in acute infections, also called HAIs.

Under these circumstances, the impact of corticosteroids on the immune system has been extensively investigated. Glucocorticoids exert a wide range of anti-inflammatory and immunosuppressive effects on multiple immune cells (figure 1). They reduce macrophage production of interleukin (IL)-1, IL-6, tumour necrosis factor-α (TNF-α), prostaglandins and leukotrienes, while also suppressing the tumoricidal and microbicidal activities of activated macrophages and neutrophils. Glucocorticoids also lead to significant decreases in lymphocyte counts and inhibit T-cell activation by suppressing IL-2, IL-3, IL-4 and IL-6. Additionally, they impair the maturation of double-positive T-lymphocytes ($CD4^+$ and $CD8^+$), which constitute the majority of thymocyte populations, due to their heightened susceptibility to glucocorticoid-induced apoptosis. Finally, they negatively impact the maturation and function of dendritic cells, which play a crucial role in initiating adaptive immune responses [20, 21].

Focusing on RCTs, it is important to highlight the early studies where steroids were administered to healthy adults to observe their effects on immune responses. In such trials, comparing prednisone to a placebo, discernible alterations in peripheral cell lines, such as peripheral white blood cells, were observed within the initial day following drug ingestion, with noticeable outcomes observed across doses of 10, 25 and 60 mg [22, 23].

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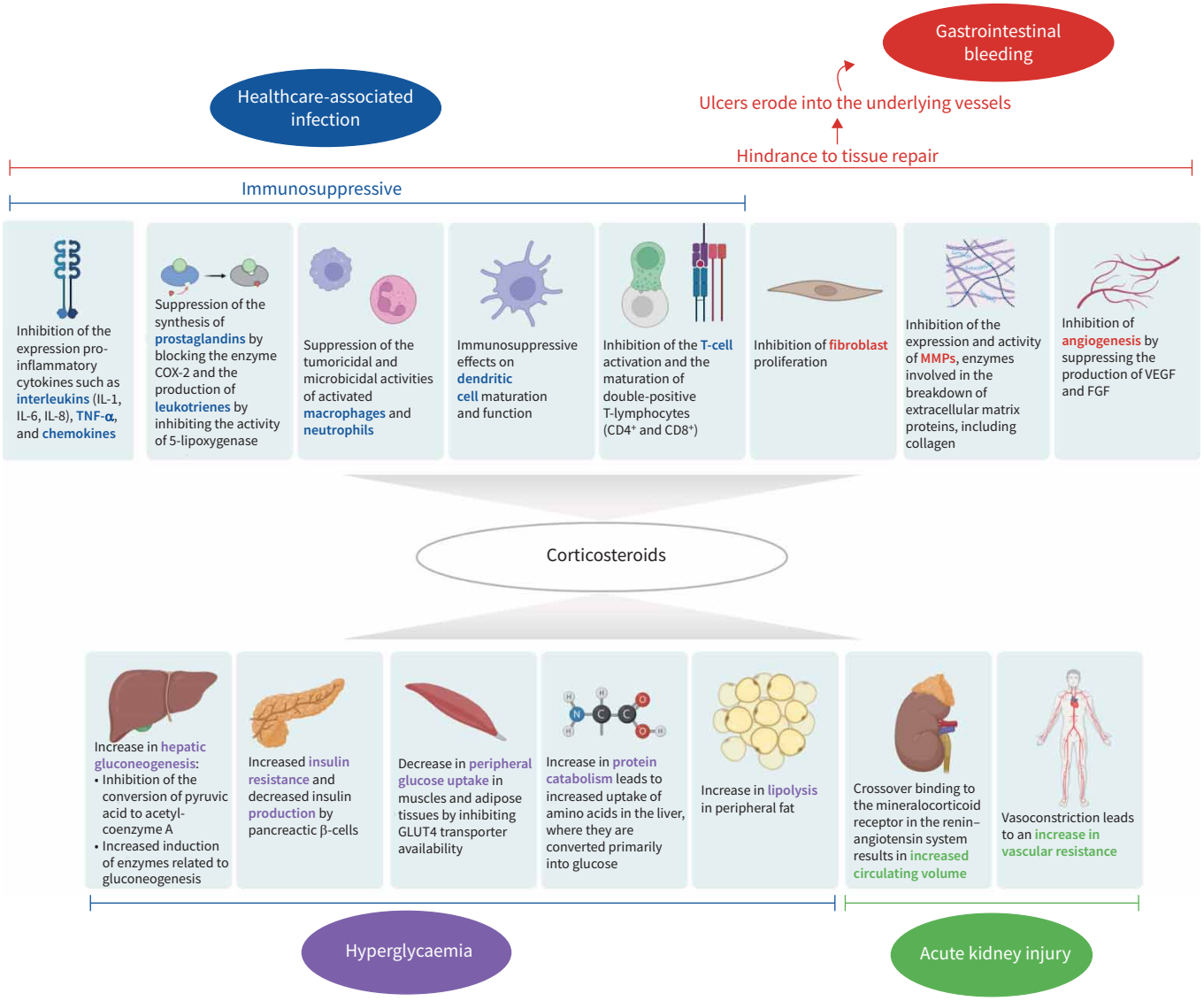
Gastrointestinal bleeding
Healthcare-associated infection
Ulcers erode into the underlying vessels
Hindrance to tissue repair
Immunosuppressive
Inhibition of the expression pro-inflammatory cytokines such as interleukins (IL-1, IL-6, IL-8), TNF-α, and chemokines
Suppression of the synthesis of prostaglandins by blocking the enzyme COX-2 and the production of leukotrienes by inhibiting the activity of 5-lipoxygenase
Suppression of the tumoricidal and microbicidal activities of activated macrophages and neutrophils
Immunosuppressive effects on dendritic cell maturation and function
Inhibition of the T-cell activation and the maturation of double-positive T-lymphocytes (CD4+ and CD8+)
Inhibition of fibroblast proliferation
Inhibition of the expression and activity of MMPs, enzymes involved in the breakdown of extracellular matrix proteins, including collagen
Inhibition of angiogenesis by suppressing the production of VEGF and FGF
Corticosteroids
Increase in hepatic gluconeogenesis:
• Inhibition of the conversion of pyruvic acid to acetyl-coenzyme A
• Increased induction of enzymes related to gluconeogenesis
Increased insulin resistance and decreased insulin production by pancreactic β-cells
Decrease in peripheral glucose uptake in muscles and adipose tissues by inhibiting GLUT4 transporter availability
Increase in protein catabolism leads to increased uptake of amino acids in the liver, where they are converted primarily into glucose
Increase in lipolysis in peripheral fat
Crossover binding to the mineralocorticoid receptor in the renin–angiotensin system results in increased circulating volume
Vasoconstriction leads to an increase in vascular resistance
Hyperglycaemia
Acute kidney injury

FIGURE 1 Biological basis of potential effects of corticosteroid treatment. COX-2: cyclooxygenase-2; FGF: fibroblast growth factor; MMP: matrix metalloproteinase; TNF-α: tumour necrosis factor alpha; VEGF: vascular endothelial growth factor.

Specifically, lymphocyte and monocyte counts decreased significantly in a dose-dependent manner within 5 h of treatment on both days 1 and 7, while eosinophil counts decreased significantly, although without a dose-dependent effect. Additionally, TNF-α showed significant dose-responsive reductions at 8 h after prednisone treatment on both days 1 and 7.

Sprung *et al.* [24] showed an increased incidence of superinfection, including new episodes of sepsis or septic shock, in patients with sepsis and septic shock who were treated with hydrocortisone, although none of the subsequent trials on corticosteroids in sepsis and septic shock reported a higher risk of superinfection [7, 25, 26].

With regard to their use in sCAP, the majority of analysed RCTs and meta-analyses [27–31] did not show an increase in the incidence of HAI in patients treated with cortisone compared to the placebo (figure 2).

The aforementioned largest randomised clinical trial on corticosteroids in sCAP, published by Dequin *et al.* [4], showed that ICU-acquired infections occurred in 9.8% of patients in the hydrocortisone group and in 11.1% in the placebo group (hazard ratio (HR) 0.87, 95% CI 0.57–1.34). The ICU-acquired infections included ventilator-associated pneumonia and bloodstream infections.

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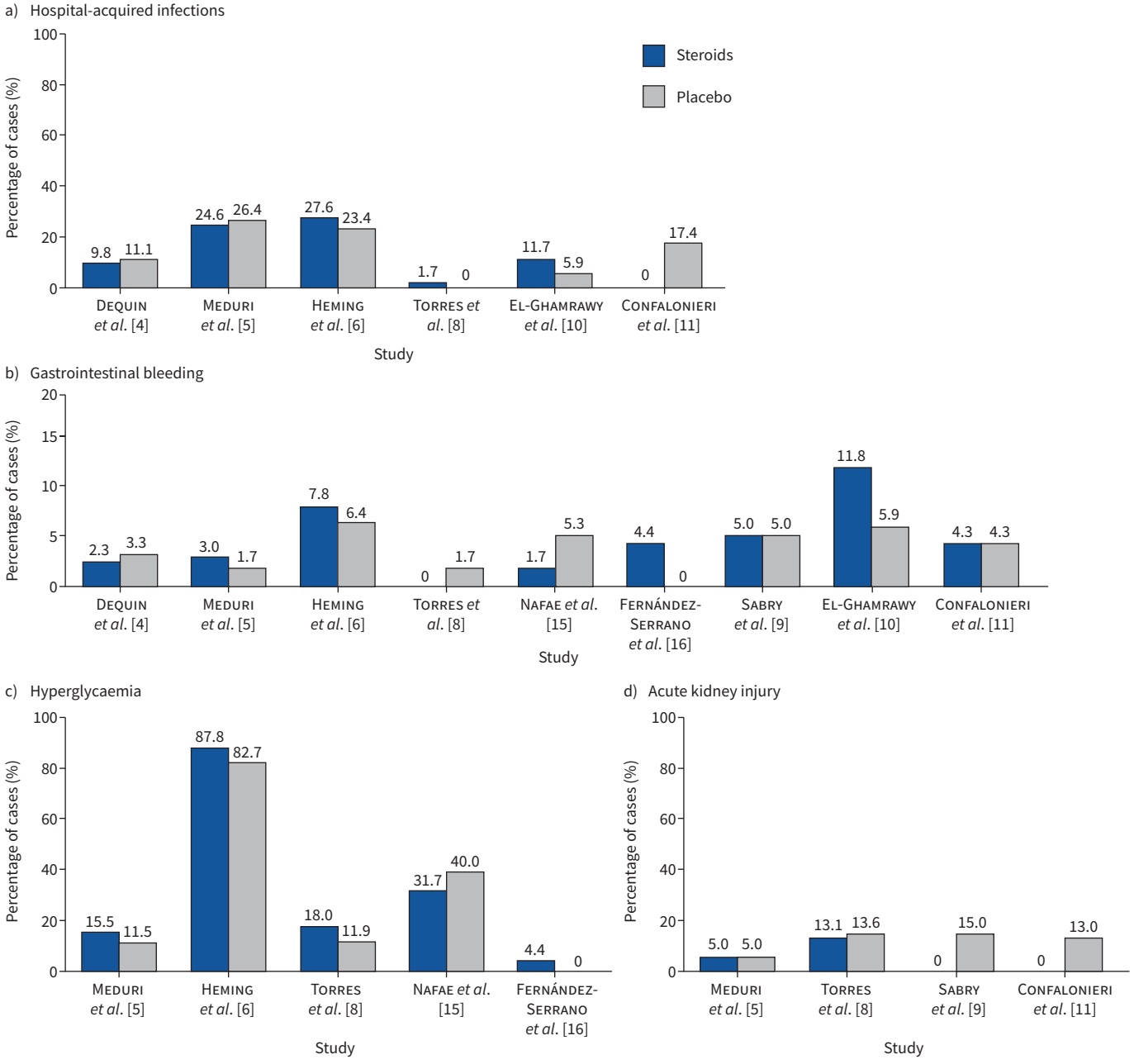

FIGURE 2 Comparison of adverse events between the study group receiving corticosteroids and the control group without corticosteroids in the analysed randomised control trials (RCTs). Percentage of each adverse event among the RCTs is also displayed at the top of the bars.

In 2020, Iqbal *et al.* [32] conducted a retrospective observational study among 508 patients admitted with a primary diagnosis of CAP in Pakistan. Among these patients, 173 (34%) received *i.v.* steroids, while 335 (66%) did not. Nosocomial infections and other complications of CAP, such as multisystem organ failure and acute respiratory distress syndrome, were observed more frequently in patients who received steroids compared to those who did not. The incidence of nosocomial infections was 10.42% in the steroid group *versus* 0.91% in the nonsteroid group ($p<0.05$).

In the meta-analysis conducted by Wu *et al.* [27] in 2023, which focused on four trials [4, 8, 10, 11], no significant difference was observed between the study and control groups in terms of HAI (relative risk 0.89, 95% CI 0.60 to 1.32; p=0.56). In their meta-analysis, Chen *et al.* [29] demonstrated that the risk for superinfection among CAP patients in the steroid treatment group was higher than that in the conventional

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treatment group (relative risk 1.25, 95% CI 0.35–4.45), although there was no statistically significant difference (Z=0.34, p=0.73).

The variability in the results can be attributed to differences in the doses administered and the duration of treatment; in the study by Sprung *et al*. [24], hydrocortisone was used for a longer treatment period, suggesting that both the dose and duration of treatment may influence the immunosuppressive effects of corticosteroids.

Additionally, in the observational study by Iqbal *et al*. [32], several factors potentially increase pneumonia complication risks among patients. These include heightened pneumonia severity in steroid-receiving patients compared to those who did not, delays in seeking medical care due to resource limitations and patients' unawareness of their comorbid conditions, often diagnosed only upon hospital admission.

Despite these findings, it remains crucial for physicians to implement prophylactic measures and maintain vigilant surveillance. This is especially important since glucocorticoid treatment diminishes the febrile response to superinfection, as indicated by the critical illness-related corticosteroid insufficiency guidelines [33].

Steroid-induced hyperglycaemia and management challenges

Hyperglycaemia is a common side-effect, occurring in approximately 50% of hospitalised patients on high corticosteroid doses [34]. While corticosteroids can counteract certain insulin effects, such as appetite reduction, they primarily induce hyperglycaemia through increased insulin resistance and decreased insulin production by pancreatic β-cells (figure 1). They directly enhance glucose production in the liver by activating genes involved in carbohydrate metabolism and indirectly by impeding insulin's metabolic actions. Corticosteroids also elevate substrate availability for gluconeogenesis and enhance gluconeogenesis processes. Additionally, they amplify the effects of counterregulatory hormones such as glucagon and epinephrine, further stimulating glucose synthesis. Finally, corticosteroids decrease peripheral glucose uptake in muscles and adipose tissues by inhibiting glucose transporter type 4 (GLUT4) availability and interfering with insulin signalling pathways [35].

Low doses of prednisolone (7.5 mg) administered daily for 2 weeks in healthy men were found to impair insulin suppression of hepatic glucose production and insulin-mediated suppression of lipolysis [36].

Kauh *et al.* [23] demonstrated that a single dose of 10 mg prednisone may acutely impair glucose tolerance. However, it remains unknown whether this acute impairment of glucose tolerance, observed after a single dose, would persist.

Patients with COPD receiving oral corticosteroids face over a fivefold risk of developing hyperglycaemia [37]. Elevated blood glucose, particularly induced by corticosteroids, is associated with a 10% increased risk of death for each 18 $mg \cdot dL^{-1}$ rise after adjusting for age, sex and diabetes mellitus [37]. Early detection of hyperglycaemia within the first 24 h in COPD-reactivated patients is linked to worse outcomes [38].

Concerning the use of corticosteroids in sCAP, an increased incidence of hyperglycaemia, which is consistent with the pharmacodynamic effects of glucocorticoids, has been reported in several trials [8, 5, 5], meta-analyses [28–30, 39–41] and in one observational study [32] (figure 2).

Hyperglycaemia was generally defined as an increase in blood glucose levels requiring the initiation or intensification of insulin therapy; however, no specific glucose threshold for diagnosing hyperglycaemia was provided.

Dequin *et al*. [4] demonstrated that patients in the hydrocortisone group received higher doses of insulin during the first 7 days of treatment.

In February 2024, Heming *et al.* [6] conducted an *a priori* planned exploratory subgroup analysis of the APROCCHSS trial [7] to investigate potential differences in responses to hydrocortisone plus fludrocortisone between CAP-related septic shock and non-CAP-related septic shock. Of the 1241 patients included in the APROCCHSS trial, 562 had a diagnosis of CAP (279 in the placebo group and 283 in the corticosteroid group) and 648 patients did not have CAP (329 in the placebo group and 319 in the corticosteroid group). They found that these corticosteroid treatments were associated with an increased risk of hyperglycaemic episodes (⩾1 episode of blood glucose levels of ⩾150 $mg \cdot dL^{-1}$ by day 7) both in

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the CAP subgroup (OR 2.17, 95% CI 1.28–3.70) and in the non-CAP subgroup but there was no statistically significant difference in this group (OR 1.51, 95% CI 0.97–2.34).

A significantly higher incidence of hyperglycaemia requiring treatment with insulin was also found in an RCT conducted by Blum *et al.* [17] in 2015, involving 802 patients hospitalised with CAP (19% *versus* 11%; OR 1.96, 95% CI 1.31–2.93; p-value: 0.001). However, the rates of new insulin treatment need at day 30 were low in both the steroid and placebo groups.

Three recent meta-analyses from 2023 [28, 30, 31] and a 2024 focused update of sCAP guidelines [42] have also shown that corticosteroid use was associated with an increased incidence of new-onset hyperglycaemic events compared with standard care.

Pitre *et al.* [31] showed that the dose–response meta-analysis for hyperglycaemia revealed both a nonlinear and linear dose–response relationship, although the nonlinear model exhibits considerable uncertainty for doses exceeding 8.5 mg of dexamethasone per 7 days. Both the nonlinear and linear models suggest increasing harm with higher doses of corticosteroids. This rise in glucose level was only transient, did not affect the clinical outcome and did not prolong hospital stay [17, 43].

In the trial conducted by Popovic *et al.* [44], higher mean glucose levels and greater glycaemic variability were observed in both diabetic and nondiabetic patients. This was a preplanned subanalysis of the RCT conducted by Blum *et al.* [17] in 2015, whose primary objective was to evaluate whether diabetes and/or hyperglycaemia on admission to the hospital influenced the effect of corticosteroids on outcomes in a well-defined cohort of patients with CAP. Of the 726 patients treated per protocol and included in this analysis (362 in the prednisone group and 364 in the placebo group), 19% had diabetes mellitus (66 in the prednisone group and 72 in the placebo group). While diabetic patients generally had higher mean glucose levels, these levels did not negatively impact the outcomes. Diabetic patients treated with prednisone did not require more additional insulin than those treated with a placebo. In contrast, nondiabetic patients receiving prednisone necessitated more additional insulin treatment [44].

Overall, these findings suggest that systemic corticosteroids are generally safe for use acutely in the treatment of sCAP; however, glucose levels should be closely monitored and appropriate management strategies should be implemented to mitigate the risk of hyperglycaemia. Most studies excluded patients at higher risk for adverse effects from corticosteroids, such as patient with uncontrolled diabetes mellitus. Application of these findings to these populations is therefore questionable.

Steroid-related GI bleeding: risk and management

Corticosteroid use was associated with increased risk of GI bleeding and perforation; the increased risk was statistically significant for hospitalised patients only [43]. The occurrence of GI bleeding and perforation is believed to result from ulcers eroding into underlying vessels (figure 1). Although the precise mechanism through which corticosteroids may induce GI bleeding or perforation remains incompletely understood, it is suggested that corticosteroids could hinder tissue repair, thereby causing delayed wound healing. Furthermore, the anti-inflammatory and analgesic effects of corticosteroids might obscure symptoms associated with gastroduodenal ulcers and ulcer complications, potentially leading to a delayed diagnosis [43]. Moreover, bleeding or perforation is also seen as complications to stress ulcers among patients with critical illness in ICUs and this could explain why the risk of GI bleeding associated with corticosteroid use is statistically significant only in hospitalised patients.

In the analysed trials and meta-analysis [27–31, 39–41], the incidence of GI complications was not increased by corticosteroid use regardless of dosage and duration of administration (figure 2). Dequin *et al.* [4], demonstrated that the occurrence of GI bleeding was rare in both groups, with an HR of 0.68 (95% CI 0.29–1.59).

In the RCT by Torres *et al.* [8], a multicentre trial conducted in 2015 in three Spanish teaching hospitals, 112 patients hospitalised with sCAP and a high inflammatory response were randomised to receive a 5-day course of *i.v.* bolus methylprednisolone ($0.5\ mg \cdot kg^{-1}$ every 12 h) or a placebo. Out of the total 112 patients, only one patient in the placebo group experienced GI bleeding.

Similarly, in the RCT conducted by Fernández-Serrano *et al.* [16] at the Hospital Universitari de Bellvitge in Barcelona, enrolling 56 patients with sCAP treated with either methylprednisolone or placebo, only one patient in the methylprednisolone group suffered a digestive haemorrhage related to an active

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peptic ulcer 12 days after inclusion in the study (3 days after treatment discontinuation). The patient responded well to a conservative approach.

In the meta-analysis conducted by Chen *et al*. [29] in 2015, which included three RCTs [11, 16, 19], the incidence of upper GI bleeding in the glucocorticoids treatment group was higher than that in the conventional treatment group (relative risk 1.98, 95% CI 0.37–10.59). However, this difference did not reach statistical significance (Z=1.36, p=0.17).

Due to the lack of evidence in literature about the bleeding risk associated with corticosteroid use, the value of antiulcer prophylaxis has been questioned. However, a survey [45] has shown that corticosteroids are still considered ulcerogenic by 82% of the 360 questioned physicians and that up to 75% of practitioners would treat corticosteroid users with ulcer prophylaxis.

Steroid-related AKI: type and frequency

Steroids can also impact on the renin–angiotensin system, leading to hypertension and altering renal perfusion, thereby contributing to the development of AKI [46]. Corticosteroids may also exert direct toxic effects on kidney tissues, leading to inflammation, fibrosis and impaired renal function [46] (figure 1). Notably, short-term use or lower doses of steroids generally entail a lower risk of adverse renal effects.

Some RCTs evaluated the potential nephrotoxic effects among adverse events (figure 2). For instance, the RCT conducted by Torres *et al*. [8] found no statistically significant difference in the incidence of AKI between patients receiving corticosteroids and those given a placebo, with occurrence rates closely aligned (14% *versus* 13%, p=0.85). Similar findings were observed in the RCT led by Meduri *et al*. [5], which was a multicentre, double-blind, placebo-controlled study conducted at 42 Veterans Affairs medical centres. In this study, methylprednisolone was administered for 21 days and AKI was observed in 3.9% of 297 patients in the steroid group and in 2.1% of 287 patients in the placebo group, with a nonsignificant p-value of 0.3.

In the multicentre RCT conducted by Confalonieri *et al*. [11] in Italy, which included 150 patients randomised to receive either hydrocortisone *i.v.* infusion or placebo for sCAP, none of the patients in the steroid group developed AKI, while only a few occurrences were observed in the placebo group. Similarly, in the RCT by Sabry *et al*. [9] conducted in Egyptian settings with 200 patients randomised to receive hydrocortisone *i.v.* infusion for 7 days or placebo for CAP, no instances of AKI were reported in the steroid group, whereas a few cases were noted in the placebo group.

Indeed, the meta-analysis by Wu *et al*. [27], which included four RCTs [5, 8, 9, 11], no significant differences were observed between the study and control groups in terms of AKI (relative risk 0.68, 95% CI 0.21–2.26; p=0.53). In this context, the use of corticosteroids in sCAP appears not to be related to AKI events.

However, none of these trials provides a detailed definition of AKI using specific criteria or diagnostic thresholds and the lack of standardised definitions makes it challenging to draw robust conclusions.

Hospital readmission rate following steroid therapy

Hospital readmission rates may be influenced by corticosteroid use, although the specific reasons for this association remain unclear. Notably, hospital readmission rates were reported in few studies, ranging from 5% to 45%.

In a systematic review and meta-analysis carried out by Briel *et al*. [40] including five RCTs [8, 11, 17, 41, 42], an increased rate of CAP-related rehospitalisation within 30 days of discharge was significantly associated with corticosteroid use (5% *versus* 2.7%; OR 1.85, 95% CI 1.03–3.32; p=0.04) [40]. This finding was replicated in 2023 by Saleem *et al*. [28], although in this case, all causes of hospital readmission were included. Conversely, in the RCT conducted by Meduri *et al*. [5] in 2022, no significant difference between the study and control groups was found regarding hospital readmission (relative risk 1.10, 95% CI 0.90–1.35; p=0.3).

Reasons for this discrepancy likely stem from variations in the definitions of patient populations and readmissions (CAP-related *versus* all-cause) across trials. The incidence and reasons for hospital readmission should be consistently reported in future RCTs, specially between 30 and 60 days after hospital discharge [40].

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Other notable side-effects of steroid use

Other adverse events related to sCAP and corticosteroid use, such as adverse cardiac events, neuropsychiatric complications, myopathy and acute hepatic failure, were rare and reported only in a minority of studies [8, 10, 11], with similar incidence between corticosteroid and placebo groups (figure 1).

In their metanalysis, Stern *et al*. [39] found no significant difference between the two arms for neuropsychiatric adverse events (relative risk 1.95, 95% CI 0.70–5.42; four trials, 1149 participants, fixed-effect model) or adverse cardiac events (relative risk 0.6, 95% CI 0.32–1.13; five trials, 1249 participants, fixed-effect model).

Long-term side-effects

The majority of studies on adjunct corticosteroids in sCAP did not extend their follow-up beyond day 30, except for the RCT conducted by Confalonieri *et al*. [11], which included a 60-day follow-up period. In this trial, survival to hospital discharge was 70% in the placebo group and 100% in the hydrocortisone group (p=0.009). Following hospital discharge, one patient from the control group was readmitted with recurrent pneumonia and died within 60 days of the initial study entry. No other complications were reported at day 60.

Moreover, in 2023, Blum *et al.* [47] conducted a pre-planned secondary analysis of the STEP trial [44], examining the 180-day outcomes of a 7-day course of prednisone (50 mg daily) *versus* placebo in approximately 800 patients hospitalised with CAP in Switzerland. The results of the analysis showed similar risks for mortality (HR 1.15, 95% CI 0.68–1.95; p=0.60) and most other secondary end-points such as hospital readmission (OR 0.75, 95% CI 0.24–2.33; p=0.62) and new hypertension at day 180 (OR 1.90, 95% CI 0.69–5.18; p=0.21). However, a significantly higher incidence of recurrent pneumonia (OR 2.57, 95% CI 1.29–5.12; p=0.007), secondary infections (OR 1.94, 95% CI 1.25–3.03; p=0.003) and new insulin dependence at day 180 (OR 8.73, 95% CI 1.10–69.62; p=0.041) was observed in the prednisone group.

The elevated risk of recurrent pneumonia and other secondary infections may result from excessive immunosuppression and increased hyperglycaemia, aligning with findings from earlier studies [44]. Concerning the higher incidence of new insulin dependence at day 180, various individual risk factors for the development of glucocorticoid-induced diabetes mellitus (GC-DM) have been identified in the literature. GC-DM is caused by several mechanisms, including insulin resistance, increased gluconeogenesis and β-cell dysfunction [48]. In this context, Katsuyama *et al*. [49] demonstrated that the dose of glucocorticoids was not statistically related to GC-DM in patients with rheumatic or renal disease who received steroid therapy. In contrast, patients with older age, higher haemoglobin A1c levels and a lower estimated glomerular filtration rate have a higher risk of developing GC-DM and require close monitoring [50].

Based on this evidence, investigating the long-term effects of corticosteroid usage remains crucial and continues to pose an ongoing challenge.

Viral sCAP and corticosteroid use

The recommendations of the latest ERS/ESICM/ESCMID/ALAT guidelines [13] on the use of steroids in sCAP associated with septic shock do not apply to patients with viral sCAP (influenza, severe acute respiratory syndrome and Middle East respiratory syndrome), based on common exclusion criteria from clinical trials.

In patients with influenza, corticosteroids have shown no benefit, as evidenced by multiple observational studies, which report significantly higher mortality and a three times higher incidence of nosocomial infection [51–54].

Systemic corticosteroids not only suppress the inflammation induced by severe influenza infections, but also increase the risk of opportunistic infections secondary to immunosuppression [55].

Bacterial or fungal infections, such as invasive pulmonary aspergillosis (IPA), secondary to influenza viral infections are common and significantly increase mortality [56].

Among the most important trials, Martin-Loeches *et al.* [57] reported that patients receiving corticosteroids had more than 200% higher risk of developing hospital-acquired pneumonia, even after adjusting for severity and potential cofounding factors in an observational cohort of ICU-admitted patients due to influenza

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A infection. In contrast, Kim *et al.* [58] reported that secondary bacterial and fungal infections did not increase after corticosteroid treatment, based on a propensity-matched case–control analysis. However, in their study, the use of antibiotics was nearly 100%, a crucial cofounding factor. A small study by a Dutch–Belgian consortium in 2018 [59] conducted a retrospective multicentre cohort study and found that IPA was diagnosed in two out of 10 patients admitted with influenza. Besides influenza, the administration of corticosteroids was also found to be a risk factor for IPA (adjusted OR 1.59, 95% CI 1.30–1.99; p<0.0001).

Moreover, a recent meta-analysis including 15 studies [51] and 6427 patients with influenza-related severe pneumonia or acute respiratory distress syndrome (ARDS) showed that corticosteroid therapy was associated with more than three times higher incidence of nosocomial infection (OR 3.15, 95% CI 1.54–6.45).

In patients with COVID-19, the evidence about the use of steroids is quite strong and there is a clear benefit to the use of corticosteroids in those patients presenting severe forms of disease, after the release of RECOVERY trial results in June 2020 [60]. However, the RECOVERY trial did not report on adverse events related to the use of steroids.

Currently, data on the impact of dexamethasone therapy on the incidence of superinfections in hospitalised severely ill COVID-19 patients are limited. The CoDEX RCT (COVID-19-associated ARDS treated with dexamethasone) [61] investigated the efficacy and safety of dexamethasone *versus* usual care in 299 patients in Brazil with COVID-19-associated ARDS. There was no significant difference in the incidence of superinfections; the number of new infections diagnosed by day 28 was 33 (21.9%) in the dexamethasone group *versus* 43 (29.1%) in the usual care group. Additionally, 12 patients (7.9%) in the dexamethasone group developed bacteraemia compared to 14 (9.5%) in the usual care group.

In their retrospective observational study of critically ill patients with COVID-19 admitted to 55 Spanish ICUs, Torres *et al.* [62] revealed that patients who received corticosteroids faced an elevated risk of both clinically suspected (OR 1.29, 95% CI 1.01–1.65; p=0.042) and microbiologically confirmed nosocomial pneumonia (OR 1.38, 95% CI 1.01–1.88; p=0.045). Likewise, Sowik *et al.* [63] showed that the use of dexamethasone in mechanically ventilated COVID-19 patients was strongly and independently associated with the occurrence of superinfections, with an adjusted odds ratio of 3.7 (95% CI 1.80–7.6, p<0.001).

In a national, multicentre, prospective cohort, White *et al.* [64] conducted evaluation of an enhanced testing strategy to diagnose invasive fungal disease in COVID-19 intensive care patients. They included 135 patients and COVID-19-associated pulmonary aspergillosis (CAPA) was diagnosed in 14.1% of cases, with a trend of the use of corticosteroids and history of chronic respiratory disease as independent risk factors that increased the likelihood of CAPA. Two other recent studies from ICU populations with COVID-19 [65, 66] reported 15% and 9% incidences of CAPA and both demonstrated an independent association to dexamethasone. In addition, a multicentre study by the COVID STEROID 2 trial group [67] using differing doses of dexamethasone in critically ill COVID-19 patients demonstrated only 3–4% of invasive fungal infections depending on dexamethasone dose.

The increased incidence of superinfections, including cases of CAPA, along with the widespread use of corticosteroids, is a matter of concern: worse outcomes have been observed in COVID-19 patients with coinfections compared to those without such complications [68]. Further studies need to be conducted to determine whether there is an association between the use of corticosteroids and the increased rate of infections in severely ill COVID-19 patients.

In relation to the occurrence of other adverse events likely associated with the use of corticosteroids in COVID-19 pneumonia, besides a more frequent occurrence of hyperglycaemia [62, 69] and a case of severe neuromyopathy [70], no other serious adverse events were reported.

Conclusions and future perspectives

Corticosteroids are generally safe for acute use in the treatment of sCAP; the analysed trials and meta-analysis suggest that they are not associated with a higher incidence of adverse effects such as HAI, GI tract bleeding and AKI. They probably increase the risk of hyperglycaemia, but close monitoring of glucose levels and appropriate management strategies should help mitigate this risk.

Taking into account the efficacy and the relative safety profile highlighted by recent RCTs, the risk–benefit profile of corticosteroids supports their use in patients with sCAP, particularly in those with elevated

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inflammatory markers and when administered early, while excluding cases of sCAP due to viral non-COVID-19 aetiology.

However, the literature appears deficient in delineating the optimal corticosteroid type for balancing potential adverse effects, as well as considering the safest dosage, duration and tapering strategies. Furthermore, further research is needed to determine the long-term effects of corticosteroid use in sCAP, given that the majority of studies did not extend their follow-up beyond day 30.

In addition, the variability in the definition and assessment of complications across trials emphasises the need for standardised criteria in future RCTs. Clear definitions for complication outcomes must be established to ensure accurate data on the safety of corticosteroids in sCAP.

Importantly, while several studies mentioned steroid-related side-effects, few explicitly examined how these effects might influence treatment responses or clinical outcomes. Addressing this gap in future research will be essential for a more comprehensive understanding of the safety and efficacy of corticosteroids in sCAP.

Regarding the characteristics of the population, the potential of classifying into certain subgroups of patients which may be more likely to suffer from undesirable effects is another important matter. In fact, most of the primary studies also excluded patients who had an underlying immune deficiency, were pregnant, had recent GI bleeding, uncontrolled diabetes mellitus or were at high risk for neuropsychiatric adverse effects. The application of these findings to these populations remains an ongoing challenge.

Questions for future research

Even though corticosteroids are potentially useful in treating bacterial sCAP, there are still a number of safety issues that remain unanswered. In particular:

- Uncertainty about which subpopulations are at higher risk of adverse effects.
- Lack of guidelines on how to monitor for potential adverse effects of corticosteroid use.
- Unclear effects of different doses and durations of corticosteroid therapy on the risk of developing HAIs.
- Need for further research on managing hyperglycaemia, including identifying the most effective methods for control.
- Limited literature on the long-term effects (beyond 30 days) of short-term corticosteroid use.
- Importance of studying the risk of 30–60-day readmission after hospital discharge.
- Need to collect prospective observational data and incorporate them into future trials.
- Lack of research on corticosteroid use in viral sCAP, particularly whether their benefits extend beyond COVID-19 to other subpopulations.

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